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Steroid Sex Hormones and Cardiovascular Function in Healthy Males and Females: A Correlational Study

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LUNDBERG, U., L. WALLIN, G. LINDSTEDT AND M. FRANKENHAEUSER. *Steroid sex hormones and cardiovascular function in healthy males and females: A correlational study.* PHARMACOL BIOCHEM BEHAV **37**(2) 325–327, 1990.—The relationship of serum estradiol and testosterone levels to systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) was examined in healthy nonsmoking males (n = 30) and females (n = 22), 30–50 years of age (mean age for men = 41.2, women = 39.9). Postmenopausal women and women taking oral contraceptives had been excluded. Testosterone levels in women were positively correlated with SBP, DBP and HR, after removing the effects of age and body mass. Positive correlations were also found between estradiol and SBP and HR in women. No systematic relationships were found between steroid sex hormones and cardiovascular measurements in men. The findings suggest a role of steroid sex hormones in cardiovascular function of women, whereas the relationship in men is less clear.

Serum estradiol Serum testosterone Blood pressure Heart rate Sex differences

THE lower incidence of coronary heart disease (CHD) in women before the menopause, compared to men of the same age, indicates that steroid sex hormones may have an effect on coronary risk factors. However, the relationships are complex. Henderson *et al.* (11) concluded that epidemiological studies of postmenopausal estrogen use suggest a moderate degree of protection from coronary artery disease, whereas Heller and Jacobs (8) stated that "the idea of male sex hormones putting men at risk is more plausible than that of female sex hormones being protective" (p. 473).

In men, estrogen treatment is known to be associated with increased risk of CHD (20,21). It has also been found that men with a history of myocardial infarction have significantly higher levels of estradiol (E2), whereas no relation was found between estradiol and extent of coronary disease as determined by angiography (19). Furthermore, serum estradiol levels in 3000 men undergoing coronary angiography did not show any significant association with the presence or degree of coronary artery disease (6). Thus, it seems as if estradiol in men is associated with risk of myocardial infarction, but not necessarily with atherogenesis. With regard to testosterone, Poggi *et al.* (17) found significantly lower plasma levels and Heller *et al.* (9) slightly higher ($p<0.10$) levels in male myocardial infarction patients compared to matched control patients.

Possible coronary risk factors involved in these relationships are blood lipids and blood pressure. In men, positive correlations have been reported between testosterone and (protective) high density lipoprotein (HDL) cholesterol (7, 10, 15), whereas Semmens *et al.* (18) found a negative correlation between testosterone and HDL cholesterol after correction for the amount of bound testosterone. Estrogens seem to reduce serum cholesterol without reducing the risk of CHD (14,16). Data on women are scarce, but Christiansen *et al.* (1) found that cyclic estrogen/gestagen administration decreased serum cholesterol and diastolic blood pressure in normal postmenopausal women.

With regard to blood pressure, estrogen treatment has been considered to contribute to elevated levels (4). However, data are not consistent and in our laboratory it was found 1) that estrogen replacement therapy (3) did not affect blood pressure (or heart rate) in postmenopausal women, 2) that blood pressure and heart rate did not change during the menstrual cycle in healthy women (2), and 3) that antiandrogen treatment of hirsute women did not affect blood pressure, but significantly increased heart rate (12).

The aim of present study was to examine the relationship of serum estradiol and testosterone levels to systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) in healthy men and women. Cardiovascular measurements were obtained both under controlled conditions in the laboratory (stress and rest,

respectively) and under natural conditions at work and at home.

METHOD

Subjects and General Procedure

The analyses were based on data from 30 men and 22 women after excluding four menopausal women (no menstruation for the last 6 months), three women taking oral contraceptives and one woman with extremely low estradiol level (0.05 nmol/l), indicating that she was postmenopausal too. The age range was 30–50 years (mean age for men = 41.2, women = 39.9). All subjects were nonsmokers and free of medication. A medical check-up confirmed that they were in good health. Body mass index was calculated from height and weight measurements.

At 8 a.m., after 12–14-hr fasting, a venous blood sample was drawn from each subject. In women, blood samples were obtained between day 10 and 14 of the menstrual cycle.

Cardiovascular measurements (SBP, DBP, HR), obtained from the same subjects and presented earlier (5,13), comprised the following four different conditions: 1) a normal day at work (mean of 9 values from 9 a.m. to 5 p.m.), 2) a work-free day at home (mean of 9 values from 9 a.m. to 5 p.m.), 3) 60-min laboratory-induced mental stress (mean of 19 values obtained during five stress tests and a Type A interview) and 4) 50-min rest in the laboratory setting (mean of 6 values). Measurements at home were obtained one week after the day at work, whereas blood samples were drawn four months later, one week before the laboratory experiment.

Hormone Assays

Serum estradiol and testosterone were determined by radioimmunoassays as outlined below. Each analyte was determined in two consecutive runs, samples from men in one and samples from women in the other. Duplicates were assayed throughout.

Serum estradiol was determined by a nonextraction radioimmunoassay (ER 155, ^{125}I-Estradiol Direct Radioimmunoassay Kit, Radioisotopenservice, Eidg. Institute Reaktorforschung, Wrenlingen, Switzerland) with a detection limit of about 0.002 nmol/l and a crossreactivity for estrone and estriol of 2%, other tested steroids crossreacting far less. The upper limit of the reference interval for men and for postmenopausal women is stated to be 0.17 and 0.20 nmol/l, respectively. Preovulatory peak reference limits are given as 0.5–1.7 nmol/l. Using serum pools from postmenopausal women and of follicular-phase samples, respectively, we found total between-assay CV's of 12% (mean 0.04 nmol/l) and 3.0% (mean 0.27 nmol/l), respectively, in 17 consecutive assay runs during one year. In the present assay runs, the within-assay CV's for volunteers' samples were 7.8% and 5.3% (range 0.0–0.7 nmol/l) and 3.1% (range 0.7–1.3 nmol/l).

Serum testosterone (+dihydrotestosterone, antiserum crossreactivity 45–50%) was determined by a single-antibody radioimmunoassay (Testosterone/Dihydrotestosterone RIA Kit, Amersham International plc, Amersham, UK) after the extraction of the serum sample with diethylether. Charcoal adsorption is used to separate free from bound ligand; radioligand is (1,2,4,5,6,7-^{3}H)testosterone. The reference interval for men (hospitalized + outpatients) is 8–42 nmol/l; the upper limit of the reference interval is 3.5 nmol/l for women. The total between-assay CV for serum pools was found to be 13% (mean 2.2 nmol/l) and 4.1% (mean 24 nmol/l) in eight consecutive runs during a 3-month period. In the present study the within-assay CV was 5.1% for women's samples and 2.4% for men's samples.

RESULTS

Steroid hormone values and measurements of height and weight are presented in Table 1. As reported earlier (5), all subjects had normal systolic (<160 mmHg) and diastolic blood pressure (<95 mmHg).

TABLE 1

MEANS, RANGES AND STANDARD DEVIATIONS OF STEROID HORMONE VALUES (nmol/l), WEIGHT (kg) AND HEIGHT (m) OF WOMEN AND MEN

	Women (n = 22)			Men (n = 30)		
	Mean	SD	Range	Mean	SD	Range
Estradiol	0.61	0.311	0.08–1.31	0.10	0.021	0.06–0.15
Testosterone	1.97	0.554	1.00–3.00	24.54	5.370	14.00–35.00
Height	1.63	0.061	1.49–1.74	1.77	0.054	1.69–1.90
Weight	57.22	4.953	45.00–66.00	79.30	7.437	65.00–95.00

After removing the (linear) effects of age and body mass (BMDP6R), partial correlations were calculated between estradiol and testosterone values and SBP, DBP and HR measurements in the four different conditions for males and females, respectively.

As shown in Table 2, testosterone levels in women were positively correlated with SBP, DBP and HR, the associations being particularly high and significant ($p<0.01$) during stress in the laboratory. Positive correlations were also found between estradiol and SBP and HR in women. No systematic relationships were found between steroid sex hormones and cardiovascular measurements in men.

DISCUSSION

The results show a significant association between testosterone and cardiovascular measurements in women. The positive association was most pronounced for the laboratory condition. The higher correlations in the laboratory could be due to the more standardized conditions compared to the real-life situation at work

TABLE 2

PARTIAL CORRELATIONS BETWEEN STEROID HORMONES VALUES AND CARDIOVASCULAR MEASUREMENTS IN WOMEN AND MEN AFTER REMOVING THE EFFECTS OF AGE AND BODY MASS

	Women (n = 22)		Men (n = 30)	
	Estradiol	Testosterone	Estradiol	Testosterone
SBP (mmHg)				
at work	0.48*	0.38	0.10	0.10
at home	0.48*	0.41	0.14	−0.07
stress	0.39	0.46*	0.01	0.07
rest	0.31	0.53*	−0.05	−0.01
DBP (mmHg)				
at work	0.28	0.31	0.11	−0.29
at home	−0.09	0.14	0.26	−0.27
stress	0.03	0.55†	0.24	−0.04
rest	0.10	0.40	−0.01	−0.24
HR (beats/min)				
at work	0.55†	0.23	−0.29	−0.18
at home	0.34	0.28	−0.16	−0.27
stress	0.47*	0.44*	−0.29	−0.30
rest	0.34	0.41	−0.22	−0.18

*$p<0.05$; †$p<0.01$.

and at home and/or to the fact that cardiovascular measurements in the laboratory and blood sampling for steroid hormone determination were obtained with a one-week interval, whereas cardiovascular measurements in the natural settings were obtained four months earlier. Table 2 also suggests an association between estradiol in women and SBP and HR, but not DBP.

The correlational nature of the present study does not permit interpretation of causal relationships. However, the consistent pattern of correlations obtained for the present group of healthy women suggests a role of steroid sex hormones in cardiovascular regulation, whereas the corresponding relationships in men are less clear.

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